47. (Amended) A method of treating an IgE mediated allergic disorder in a human subject comprising administering an effective amount of an anti-human CD23 antibody comprising a human gamma-1 constant region.

REMARKS

Entry of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 CFR 1.116, and in light of the remarks which follow are respectfully requested.

Turning now to the Office Action, Claim 46 stands rejected as allegedly not being enabled by the teachings of the application. This rejection is respectfully traversed based on the amendment of Claim 46 to refer to SEQ ID NO's for the particular variable heavy and light domains of the exemplified anti-human CD23 antibodies. Therefor, as the claim does not refer to the monoclonal antibody by antibody designation number, nor is a particular antibody required for enablement, withdrawal of the deposit requirement is respectfully believed to be in order.

Claims 38-47 stand rejected under 35 USC 112, first paragraph, as being broader than the enabling disclosure. Essentially, the Examiner indicates that the subject anti-human CD23 antibodies can be used to inhibit IgE in vivo and thereby treat allergic IgE mediated disorders. However, the Examiner disputes whether this will correlate to all types of diseases encompassed by the claims.

This rejection is respectfully but strenuously traversed, especially in view of the present amendments. Most of the subject claims, i.e. Claims 38-46, are directed to a method for inhibiting IgE in vivo by administration of an anti-human CD23 antibody having human gamma-1 constant regions. The Examiner has conceded on the record that antibodies according to the invention possess IgE inhibiting activity in vivo. Hence, there is absolutely no basis for maintaining the §112 enablement rejection against Claims 38-46. Essentially, in construing enablement, the Examiner must consider the claim limitations and determine whether such limitations are sufficiently taught by the teachings of the application.

Herein, there is absolutely no basis for disputing enablement absent a convincing reason that the claimed methods will not work *as claimed.* Herein, the Examiner *cannot* meet this burden by her own admissions unless she attempts to read limitations into the claims which are not explicit or implicit in the claims under examination.

Withdrawal of the enablement rejection as it pertains to Claims 38-46 is therefore respectfully requested.

Claim 47 stands rejected under 35 USC 112, first paragraph, as being non-enabled. This claim has been amended herein to recite precisely what the Examiner has stated is enabled, namely treatment of allergic IgE mediated disorders using anti-human CD23 antibodies according to the invention. Withdrawal of the enablement rejection against Claim 47 is also respectfully requested.

Also, the §112 enablement rejection is respectfully traversed based on the §132 Declaration by Richard G. Lizambri provided herewith. This declaration provides additional evidence relating to the IgE inhibitory activities of antibodies according to the invention.

Claim 46 stands rejected under 35 USC 112, second paragraph as being indefinite. This rejection is not addressed as it is moot in view of the present amendments.

Claims 38, 40-45 and 47 stand rejected under 35 USC 102(a) as allegedly being anticipated by Bonnefey (WO 96/12741) in view of Saxon et al. (*J. Immunol.* 147(11): 4000-6 (1991)). This rejection is respectfully traversed.

Essentially the position of the Examiner is that Bonnefey teaches all elements of the claimed methods and therefor is an appropriate anticipatory rejection. This rejection is respectfully traversed.

Applicants respectfully submit that Bonnefey does not anticipate the claimed methods given the myriad of different possible CD23 agonists and antagonists that are disclosed in the reference coupled with the numerous potential applications thereof for both therapy and diagnosis.

In particular, the reference discloses that potential CD23 agonists and antagonists include antibodies, small molecules and fusion proteins. With respect to antibodies, the reference further discloses that such antibodies include by way of example intact antibodies, antibody fragments including Fab, Fab_2, and Fv, single chain antibodies, chimeric antibodies and humanized antibodies. Also, with respect thereto, the reference further discloses that such antibodies may comprise human constant domains selected from gamma 1, gamma 2, gamma 3 and gamma 4.

With respect to potential utilities of such ligands, the reference teaches a variety of potential applications including treatment of allergic disorders, autoimmune disorders and inflammatory disorders.

Thus, Applicants respectfully submit that the reference does not provide the requisite specific incentive to specifically select as the CD23 antagonist or agonist an anti-human CD23 antibody that comprises specifically human gamma 1 constant domains and to use same to inhibit IgE in a human subject.

Rather, at best, as previously argued, the reference should have been applied under 35 USC 103, because to arrive at the claimed methods, one is required to "pick and choose" among a myriad of different possibilities with no specific incentive to select the method chosen by Applicants. In fact, as substantiated by a reference of record, Flores-Romeo et al., *Science* 261:1038-1046 (1993), the more logical selection for therapy would have been an antibody fragment, i.e. a Fab fragment, give the thinking at the time of the invention and the time that Bonnefey was published that the IgE inhibiting activity of anti-CD23 antibodies did not reside in their effector function, as evidenced by the fact that Fab fragments prepared from anti-CD23 antibodies effectively inhibited antigen-specific IgE production in the rat. It would have been anticipated that these results would correlate to human subjects absent evidence to the contrary, and moreover, that antibody fragments would be preferred because of reduced potential to induce immunogenicity and reduced potential to interact with Fc receptors, which the prior art would suggest to be non-significant to functionality.

The fact that Saxon et al. discloses that anti-CD23 antibodies inhibit IgE expression does not support the rejection. Again, this does not substantiate a

conclusion that one of ordinary skill would have been specifically motivated to select an anti-human CD23 antibody containing human gamma 1 constant domains for therapy. As discussed above, and substantiated by Flores-Romeo, the skilled artisan would have had a disincentive to select antibodies of this specific nature, especially given Flores-Romeo.

Therefore, withdrawal of the §102 rejection based on Bonnefey and Saxon et al. is respectfully requested.

Claims 38-45 and 47 further stand rejected under 35 USC 103 as being unpatentable over Bonnefey et al. (WO 96/12741) in view of Saxon et al. (*Id.*) and Newman et al. (U.S. Patent 5,658,570). This rejection is respectfully traversed for substantially the same reasons as supra in the rebuttal of the §102 rejection. The addition of the Newman patent does not cure the deficiencies of the rejection.

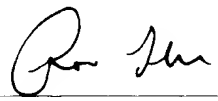
While this patent discloses the advantages of primatized antibodies to human antigens, including a variety of antigens, among which specifically named are CD23, the reference is deficient as it fails to suggest the intrinsic advantages of anti-CD23 antibodies having gamma 1 effector function for therapy. It is hypothesized by the present inventors that this may be attributable, at least in part, to the depleting properties of antibodies according to the invention. In particular, it is hypothesized that IgE levels are reduced, at least in part, because the subject antibodies deplete circulating B cells, and thereby reduce antibody production.

In any event, Applicants respectfully maintain that the cited references, alone or in combination, fail to teach or suggest the enhanced results achieved by the claimed in vivo methods, i.e. substantial IgE inhibition vis-a-vis anti-CD23 antibodies

containing different or no constant domains. Therefore, withdrawal of the §103 rejection based on the cited references is respectfully requested.

Respectfully submitted,

PILLSBURY WINTHROP LLP



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MARK-UP COPY OF CLAIMS

38. (Amended) A method of inhibiting [treating or preventing a disease condition wherein inhibition of] IgE in a human subject in need of such inhibition comprising administering an IgE inhibiting [is therapeutically or prophylactically beneficial comprising administering an] effective amount of an anti-human CD23 [monoclonal] antibody comprising a human gamma-1 constant region [that inhibits IgE expression].

46. (Amended) The method of Claim 38, wherein the anti-human CD23 [monoclonal] antibody comprises a variable heavy domain[s derived from 5E8, 6G5 or 2C8] having a sequence selected from the group consisting of the polypeptide encoded by a nucleic acid sequence having SEQ ID NO:3, SEQ ID NO:7; and a variable light domain having a sequence selected from the group consisting of the polypeptide encoded by a nucleic acid sequence having SEQ ID NO:1 and SEQ ID NO:5.

47. (Amended) A [The] method [of Claim 38, wherein the disease condition is an allergic disorder] of treating an IgE mediated allergic disorder in a human subject comprising administering an effective amount of an anti-human CD23 antibody comprising a human gamma-1 constant region.